REMARKS

Claims 11-49 are pending in the present application.

The rejection of Claims 11, 14-15, and 17-18 under 35 U.S.C. §103(a) over Rovee et al. (U.S. 4,185,100) in view of Hettche et al. (U.S. 5,415,853) or Cutie (U.S. 5,891,419) is obviated by amendment.

Rovee et al. relates to a pharmaceutical composition for topical treatment of skin disorders. The topical vehicle may be a cream, lotion, gel or other form acceptable for topical use. Substantially, the disclosure of Rovee et al. relates to compositions that are a liquid preparation for topical administration and contain one or more solvents, including ethanol and propylene glycol (see, for example, column 3, lines 25-26, Table A, and Table B). However, preparations for topical administration do not contain propellants.

Antioxidants are only disclosed in column 4, lines 41-44 and column 5, lines 45-49 in connection with the preparation of a topical cream of oil in water emulsion type and aqueous/alcoholic solutions, respectively.

In regard to the propellants, the Examiner points to the Table under sub-heading "F. Aerosol" appearing in column 7. In sub-heading "F. Aerosol" Rovee et al. disclose that aerosol formulations can be obtained in accordance with their invention. To this end, Rovee et al. state that a propellant may be used. However, the only propellant disclosed therein is the propellant appearing in the Table that provides the composition for a quick breaking alcoholic foam. The vehicles can vary with the type of the propellant and of the concentrate, which can contain from about 8.5 to 50.0% of water. A preservative can be added, but antioxidants are not mentioned at all.

Moreover, Rovee et al. provides compositions of triamcinolone acetonide in a solvent system constituted of propylene glycol/ethanol 50/50 by volume, but does note specifically disclose or suggest triamcinolone acetonide with a propellant or specifically disclose or suggest HFA propellants at all.

In an attempt to compensate for the deficiency in the disclosure of Rovee et al. the Examiner cites in the alternative Hettche et al. and Cutie. However, Applicants submit that the present invention would not be obvious regardless of how one combines the disclosures of Rovee et al., Hettche et al., and Cutie.

Hettche et al. specifically point out the disadvantages of non-chlorinated fluorohydrocarbon propellants (column 2, line 15) in order to prepare stable aerosol *suspensions* (column 2, line 21) and provide compounds, polyoxyethylene glyceryl oleates, suitable as *suspension* stabilizers (see, for example, col 3, lines 11 and 17). However, Hettche et al. *teach away* from preparing aerosol formulations wherein the active substance is *completely dissolved* (see column 2, lines 27-30) as presently claimed. MPEP §2141.02 states: "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Therefore, in view of the disclosure by Hettche et al that it is undesirable for the dissolution, Applicants submit that Hettche et al cannot affect the patentability of the claimed invention and cannot compensate for the deficiencies in the disclosure of Rovee et al. Therefore, this combination of references fails to support a prima facie case of obviousness.

Similarly, Cutie fails to compensate of the deficiencies in the disclosure of Rovee et al. and, as such, the present invention is not obvious in view of this combination of references.

Cutie discloses flunisolide aerosol formulations wherein flunisolide is ***dispersed*** in the propellant (column 3, line 35) and wherein the cosolvent (ethanol) merely aids in ***dispersing*** the drug (column 4, line 5). Cutie widely expounds the difficulties inherent in the preparation of aerosol formulations with HFA propellants (column 1, lines 44-60) and discourages the use of a co-solvent in solution formulations, to enhance drug dissolution, in that "this practice may have the disadvantage of decreasing the fraction of the metered dose which may be inhaled and contributing to particle size growth" (column 1, lines 60-65). However, in the presently claimed invention, the corticosteroid is required to be ***completely dissolved*** in the propellant vehicle (see Claims 11, 19, and 26). This is neither disclosed nor suggested by the combined disclosures of Rovee et al. and Cutie.

In view of the foregoing, Applicants request withdrawal of this ground of rejection.

The rejection of Claims 11 and 15-23 under 35 U.S.C. §103(a) over Keller et al. (WO98/34595) is obviated in part by amendment and traversed in part.

Keller et al. disclose a pressure-liquified propellant mixture for aerosols, where the propellant mixture contains as ***required*** ingredients a fluorinated alkane (e.g., 1,1,1,2-tetrafluoroethane and/or 1,1,1,2,3,3,3-heptafluoropropane) ***and*** carbon dioxide (see, for example, Abstract, page 5, lines 23-25, and the claims). Such a disclosure is distinct from the aerosol formulation as presently claimed in which the propellant vehicle used to dissolve the corticosteroid consists of one or more hydrofluoroalkanes and a cosolvent. Accordingly, the propellant vehicle of the present invention *excludes* carbon dioxide, which is a required component in the propellant mixture of Keller et al. As such, Applicants submit that Keller et al. does not render obvious the presently claimed invention.

Further, with respect to the disclosure of Keller et al., Applicants note that this disclosure points out the various disadvantages associated with the use of the HFA propellants, in particular with respect to the preparation of suspension formulations (see from column 2, line 61 to column 3, line 52). One important disadvantage of the HFAs is their low dissolving power in comparison to the old CFC propellants (column 3, lines 7-9), which can be increased by addition of polar solvents, such as, for example, ethanol. However, Keller et al. caution that in ethanol-containing solution aerosols problems often occur relating to the active compound stability (column 4, lines 62-64).

Keller et al. solve the foregoing "problems" by using a propellant mixture based on carbon dioxide (column 5, lines 23-25) allowing for improvements of the characteristics of both suspension and solution aerosols. At column 10, lines 32-34, Keller et al. declares in general terms that the aerosol formulations can further contain buffer substances or stabilizers such as vitamin E, without making specific reference to solutions or suspensions. However, Keller et al specifically disclose the indispensable use of carbon dioxide to prepare solution aerosols having improved storage stability.

The present invention offers an alternative solution to the preparation of corticosteroid solution formulations in an HFA propellant as disclosed by Keller et al. Specifically, the present invention provides a solution by adding an antioxidant to the propellant vehicle where the propellant vehicle only consists of one or more hydrofluoroalkanes and a cosolvent (i.e., excludes carbon dioxide).

In view of the foregoing, Applicants submit that the present invention is not obvious in view of the disclosure of Keller et al. Therefore, withdrawal of this ground of rejection is requested.

The rejections of: (a) Claims 11, 16-19, 21-23, 26, and 28-30 under 35 U.S.C. §103(a) over Cutie (U.S. 5,891,419), and (b) Claims 12-15, 20, 24, 25, 27, 31, and 32 under 35 U.S.C. §103(a) over Cutie (U.S. 5,891,419) in view of Radhakrishnan et al. (U.S. 5,192,528), are obviated in part by amendment and traversed in part.

Cutie discloses aerosol formulations for oral inhalation containing flunisolide ***dispersed*** in HFC 134a and/or HFC 227 (see Abstract). The aerosol formulations disclosed by Cutie are free of CFCs and surfactants, and contain little or no ethanol. In regard to the small amounts of ethanol, Cutie discloses at column 4, lines 5-16 that ethanol is present to ***prevent dissolution*** of the flunisolide. However, this disclosure is directly at odds with the present invention wherein a cosolvent (e.g. ethanol) is used to *dissolve* the active ingredient in the propellant (see, for example, pages 10-12 and the Examples). From this disclosure by Cutie, it is clear that ethanol is not a cosolvent as used in the present invention as its function in the aerosol formulation is substantially different from that of a cosolvent, which is presently claimed.

In the outstanding Office Action, the Examiner states that this ground of rejection was maintained because "there is no requirement for the active agent to be dissolved." However, in the presently claimed invention, the corticosteroid is required to be ***completely dissolved*** in the propellant vehicle (see Claims 11, 19, and 26). Therefore, Applicants again submit that the disclosure of Cutie falls far short of disclosing or suggesting the claimed invention.

Further, Cutie widely expounds the difficulties inherent in the preparation of aerosol formulations with HFA propellants (column 1, lines 44-60) and discourages the use of a co-solvent in solution formulations, to enhance drug dissolution, in that "this practice may have the disadvantage of decreasing the fraction of the metered dose which may be inhaled and

contributing to particle size growth" (column 1, lines 60-65). As such, Cutie favors avoiding that which the present invention claims.

Applicants again note that MPEP §2141.02 states: "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). In view of the disclosure at column 4, lines 5-16, Applicants note that Cutie teaches away from the inclusion of ethanol as a cosolvent and/or the complete dissolution of the corticosteroid in the propellant vehicle. Therefore, the disclosure by Cutie fails to render the present invention obvious.

The Examiner cites Radhakrishnan et al. as disclosing specific antioxidants and budesonide. However, Radhakrishnan et al. fails to compensate for the deficiency note above for Cutie. Moreover, Applicants note that the formulation disclosed by Radhakrishnan et al. is in the form of an *aqueous liposome suspension.* Such a formulation is physically distinct from the formulation of the present invention, as well as Cutie, which is an aerosol formulation. As such, there would be no motivation to combine the disclosures of Cutie and Radhakrishnan et al.

Applicants note that the mere fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness (MPEP §2143.01). Applicants remind the Examiner that "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under 103, teachings of references can be combined *only* if there is some suggestion or incentive to do so." (*In re Fritch* 23 USPQ2d 1780, 1783 (Fed. Cir. (1992)). In view of the differences noted above in the type of formulation disclosed in Cutie (aerosol) and Radhakrishnan et al. (aqueous liposome suspension), Applicants note that absent a

specific suggestion or incentive in the references themselves their would be no motivation to combine the disclosures of Cutie and Radhakrishnan et al. As such, the present invention is not obvious in view of the disclosures of Cutie and Radhakrishnan et al.

Withdrawal of this ground of rejection is requested.

Applicants respectfully request that the provisional obviousness-type double patenting rejection of Claims 11-32 over the claims 1-13 of U.S. 10/244,519 be held in abeyance until an indication of allowable subject matter in the present application. If necessary, a terminal disclaimer may be filed at that time. Until such a time, Applicants make no statement with respect to the propriety of this ground of rejection.

However, Applicants remind the Examiner that, with respect to a provisional double patenting rejection between co-pending applications, MPEP §804 states:

> If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.

Accordingly, if the present amendment places the elected claims in condition for allowance, Applicants note that the provisional obviousness-type double patenting rejection over U.S. 10/244,519 should be withdrawn if that application is not in condition for allowance.

Applicants respectfully submit that the above-identified application is now in condition for allowance, and early notice of such action is earnestly solicited.

Respectfully submitted,

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